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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SASAN, ARADHANA	
ART UNIT	**PAPER NUMBER**
1615	

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10/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/817,306	KOCHERLAKOTA ET AL.	
	Examiner	Art Unit	
	Aradhana Sasan	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 08/09/2007 are acknowledged.

2. Claims 1 and 13 were cancelled.

3. Claims 2-7 and 10-11 were amended.

4. Claims 2-12 are included in the prosecution.

Response to Arguments

Objection to the Specification

5. Applicant's corrections of the informalities in the specification are acknowledged. The objections to the specification are withdrawn.

Objection to claims

6. In light of applicant's correction of claim numbering, the objection to claim numbering is withdrawn.

7. In light of applicant's corrections, the objection to claims 4-7 is withdrawn.

Rejection of claims 1-2, and 13 under 35 USC § 103(a)

8. Applicant's arguments, see Page 7, filed 08/09/2007, with respect to the rejection of claims 1-2, and 13 under 35 USC § 103(a) as being unpatentable over Begum et al. (US 4,713,246), in view of Crison et al. (US 5,993,858) have been fully considered but are not persuasive.

Applicant argues that no meaningful combination can be made from the teachings of the cited documents. While it is acknowledged that different drugs behave differently in combinations with different formulation excipients, and that

interchangeability of drugs in specific formulations is quite rare, the combination of the references is justifiable because Begum specifically "addresses the problem of reduced bioavailability of the capsule dosage form, and provides a liquid formulation of sufficiently high concentration for encapsulation which affords bioavailability upon ingestion equal to the intravenous solution" (Col. 2, lines 4-9). Begum discloses etoposide and a solvent (the drug phase of instant claim 2) (Col. 5, lines 5-10). The supporting reference, Crison, also addresses the problem of increasing the bioavailability of a drug and provides a self-microemulsifying formulation as a solution. In particular, Crison discloses the advantages of "increasing the dissolution and bioavailability of ... poorly water-soluble drugs ..." (Col. 2, lines 48-51). Crison also discloses "the use of microemulsions as oral drug delivery systems ... to spontaneously form (emulsify) at a given temperature, their considerable solubilizing properties, the ability to be sterilized by filtration, and high physical stability ... another desirable feature of these mixtures is their ability to form a microemulsion when exposed to gastrointestinal fluids. This type of behavior makes SMEDDS (self micro emulsifying drug delivery system) good candidates for vehicles for the oral delivery of lipophilic or slightly water-soluble drugs" (Col. 2, lines 12-20). One skilled in the art would know that etoposide is a poorly water-soluble drug. Therefore, one skilled in the art would use the liquid formulation of etoposide that can be encapsulated for addressing the problem of reduced bioavailability (as taught by Begum) and combine it with the advantages of the self micro emulsifying system for increasing the bioavailability of poorly water-soluble drugs (as taught by Crison) and arrive at the instant invention.

Applicant argues that there is no direction toward making a combination of teachings from the two documents that meets the limitations of claim 2 and that without such direction, a large number of experiments would have to be performed for any useful etoposide formulation results. Applicant states that there can be no reasonable expectation that such experimentation would be successful. However, given the teachings of the self-micro emulsifying systems of Crison, and the liquid formulation of etoposide of Begum, one skilled in the art would not need undue experimentation to use etoposide in the formulation.

Applicant states that there is no teaching or suggestion in the cited documents to modify or combine the teachings. As mentioned above, the motivation to combine the references is provided by the teachings that address the problem of reduced bioavailability by both Begum (liquid formulation for etoposide that can be encapsulated) and Crison (self micro emulsifying systems for poorly water-soluble drugs) respectively.

Therefore, the rejection of 4/10/07 is maintained.

Rejection of claims 3-12 under 35 USC § 103(a)

9. Applicant's arguments, see Page 8, filed 08/09/2007, with respect to the rejection of claims 3-12 under 35 USC § 103(a) as being unpatentable over Begum et al. (US 4,713,246), in view of Crison et al. (US 5,993,858) and further in view of Kaplan et al. (US 4,772,589) and Hauer et al. (US 5,342,625) have been fully considered but are not persuasive.

Applicant argues that neither the Kaplan patent nor the Hauer patent, nor the patents taken together, overcomes the deficiencies of the Begum/Crison combination

for establishing obviousness. Applicant states that Kaplan does not discuss a need for any surfactants, co-solvents, or anything else in their formulations, and making combinations that include such substances would not be a logical extension of the teachings.

However, the motivation to used the Kaplan reference is provided by the teaching that etoposide is suitably soluble in NMP (Kaplan, Col. 2, line 66). The improvement of bioavailability is the motivation provided by both Begum and Crison. Instant claim 2 uses the transitional phrase "comprising" for the composition, the drug phase, and the emulsifying base, which allows one skilled in the art to choose the components of the emulsifying system (solvents, co-solvents, lipids, surfactants, and stabilizers which are known in the art) according to the desired release profile, bioavailability and stability.

In response to applicant's argument that one cannot pick and choose isolated teachings from various cited documents, and then combine the teachings to make a case for obviousness, the motivation to combine the references is discussed above.

Applicant argues that Kaplan does not pertain to self-microemulsifying compositions. However, Kaplan is used as a supporting reference to supplement the teaching of self-microemulsifying compositions by Crison.

Applicant argues that whether or not all of the claim-recited ingredients are known in the art is not particularly relevant to the question of obviousness, absent some suggestion or motivation to assemble the specific combinations required by the claims.

All the claimed elements are found in Begum, Crison, Kaplan, and Hauer. One skilled in the art could have combined the elements and the combination would have yielded predictable results. See *KSR International Co. v. Teleflex Inc.*, 550 U.S. - , 82 USPQ2d 1385 (2007).

Therefore, the rejection of 4/10/07 is maintained.

NEW OBJECTIONS:

Claim Objections

10. Claim 5 objected to under 37 CFR 1.75 as being a substantial duplicate of claim 4. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

MAINTAINED REJECTIONS:

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Begum et al. (US 4,713,246), in view of Crison et al. (US 5,993,858).

The claimed invention is a self micro-emulsifying composition comprising etoposide encapsulated in a capsule shell. The composition comprises (i) a drug phase

comprising etoposide and a solvent, (ii) a co-solvent, and (iii) an emulsifying base comprising a lipid, a surfactant, and a stabilizer.

Begum et al. teaches a liquid dosage form of etoposide to be administered in capsule form (Abstract). A liquid formulation "of sufficiently high concentration for encapsulation" is disclosed and this formulation "affords bioavailability upon ingestion equal to the intravenous solution" (Col. 2, lines 4-9). The liquid dosage "composition with etoposide results in markedly improved absorption of the drug following ingestion of the composition. It is believed that this is due to the formation of a micellar solution of etoposide on dilution thereof with the gastric contents" (Col. 2, lines 14-18). The etoposide is mixed with a solvent polyethanol glycol 300 and the composition includes citric acid (Col. 5, lines 5-10).

Begum et al. does not expressly teach a self-microemulsifying composition comprising etoposide.

Crison et al. (US 5,993,858) teaches a self-microemulsifying formulation for increasing the bioavailability of a drug, which includes an emulsion including an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant (Abstract). The preferred HLB range for the hydrophilic co-surfactant is between approximately 10 and 14 (Col. 4, lines 31-33). The co-surfactants used include LABRASOL (Gattefosse Corporation), which are caprylocaproyl macrogolglycerides, LABRAFAC (Gattefosse Corporation), which are medium chain triglycerides, glycerylesters, fatty acid esters, and polyoxyethylene derivatives (Col. 4, lines 4-14, and lines 37-40).

A person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the liquid etoposide composition of Begum with the self-microemulsifying formulation of Crison. The motivation to combine these references is provided by the teaching that these compositions can form microemulsions "when exposed to gastrointestinal fluids" (Col. 2, lines 16-18). The self-microemulsifying composition would provide "a method of increasing dissolution and bioavailability of ... poorly water-soluble drugs..." (Col. 2, lines 48-51).

13. Claims 3-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Begum et al. (US 4,713,246), in view of Crison et al. (US 5,993,858), and further in view of Kaplan et al. (US 4,772,589) and Hauer et al. (US 5,342,625).

The teachings of Begum and Crison are stated above.

Begum and Crison do not teach 1-methyl-2-methylpyrrolidone or dimethyl isosorbide as solvents of etoposide and the specific components of the emulsifier base.

Kaplan et al. (US 4,772,589) teaches a stable solution of etoposide in 1-methyl-2-pyrrolidinone, and solutions having etoposide concentration as high as 500 mg/ml used to fill gelatin capsules (Abstract). Kaplan also discloses dimethylisosorbide as a possible solvent for etoposide (solubility 320 mg/ml) (Col. 3, Table III).

Hauer et al. (US 5,342,625) teaches pharmaceutical compositions of cyclosporins in microemulsion form. The preferred ether components used in the composition include glycofurol (Col. 14, lines 29-33). The composition contains surfactant, co-solvents or thickening agents (Col. 14, lines 33-35). Hauer teaches

polyalkylene glycol ethers (Col. 11, lines 59-63). Also taught are lipids, "propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate," and "propylene glycol caprylic-capric acid diester" (Col. 10, lines 60-68). Fatty acid triglycerides, ... medium chain triglycerides, and neutral plant oils are also taught (Col. 8, lines 65-68). Surfactants such as sorbitan fatty acid esters (propylene glycol laurate, are taught (Col. 11, lines 53-58). Furthermore, Hauer teaches anti-oxidants in the composition, "in particular, a tocopherol, is particularly advantageous" (Col. 13, lines 44-50).

A person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the liquid etoposide composition of Begum with the self-microemulsifying formulation of Crison, and further combine the etoposide solvent teaching of Kaplan. The motivation to use the Kaplan reference is provided by the fact that "etoposide is suitably stable in NMP" (n-methyl-pyrrolidone or 1-methyl-2-pyrrolidone) (Col. 2, line 66). The co-solvent glycofurol is taught by Hauer and would be an obvious alternative as a co-solvent for etoposide, which is a poorly soluble drug. Also, the co-solvent diethyleneglycol-mono-ethylether is a polyalkylene glycol ether and would be obvious to one skilled in the art. The solvents, co-solvents, lipids, surfactants, and stabilizers of the claimed invention are known in the art and a person could choose the components according to the desired release profile, bioavailability and stability.

Regarding instant claims 4 and 5, which recite the weight percentages of etoposide, solvent, co-solvent, and emulsifying base, a person skilled in the art would modify the percentages of the composition based on the required dosage and desired

release profile, and the recited percentages are obvious variants unless there is evidence of criticality or unexpected results.

Regarding instant claim 11, Kaplan teaches etoposide and N-methyl-pyrrolidone. Hauer teaches diethyleneglycol monoethyl ether, plant oils (instant claim recites polyoxyl 35 castor oil), polyoxyethylene-sorbitan-fatty acid esters (TWEEN) (instant claim recites polysorbate 20), and propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate. Crison teaches medium chain triglycerides, caprylocaproyl macrogolglycerides, and glyceryl esters. Therefore, all the claim limitations are taught by the references and would be obvious to one skilled in the art.

Regarding instant claims 12, Begum in view of Kaplan teaches etoposide, citric acid, and n-methyl-pyrrolidone. Hauer teaches diethyleneglycol monoethyl ether, plant oils (instant claim recites polyoxyl 35 castor oil), polyoxyethylene-sorbitan-fatty acid esters (TWEEN) (instant claim recites polysorbate 20). Therefore, all the claim limitations are taught by the references and would be obvious to one skilled in the art.

Conclusion

14. No claims are allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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